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NIKOLAI & MERSEREAU, P.A.
900 SECOND AVENUE SOUTH
SUITE 820
MINNEAPOLIS, MN 55402

EXAMINER	
SHIN, DANA H	

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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,664	JENKINSON ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008 and 22 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-78* is/are pending in the application.

4a) Of the above claim(s) *58,59 and 72-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-57,60-71,77 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-14-05, 11-16-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of claims 48-71 and 77-78 drawn to a method of promoting apoptosis and a species of MAD1, Bcl2, and SV40 in the reply filed on June 27, 2008 and July 22, 2008 is acknowledged. The traversal is on the ground(s) that all claims are sufficiently related to one basic concept and therefore should be examined together. This is not found persuasive because applicant did not identify what constitutes the "one basic concept". Further, as indicated in the Office action dated May 1, 2008, the claims pending in the instant application are found to lack unity of invention because they are drawn to multiple processes and multiple products, which do not fall within the combination of categories set forth in 37 CFR 1.475(b).

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Currently, claims 48-78 are pending in the instant application. Claims 58-59 and 72-76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Accordingly, claims 48-57, 60-71, and 77-78 pertaining to a method of promoting apoptosis drawn to a species of MAD1, Bcl2, and SV40 are currently under examination on the merits.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on October 14, 2005 and November 16, 2007 is being considered by the examiner, except WO 01/14737 A1, which discloses a fuel injection system for an internal combustion machine. The disclosure of WO 01/14737 A1 is not only unrelated to the instantly claimed invention but it is also in non-English language. Further, GenBank Accession number references are not considered because they lack appropriate publication dates.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See pages 24-25. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

Claims 48 and 61 are objected to because of the following informalities:

1) There is a large blank area in line 9 of claim 48, which contains only two words "polypeptide or". Further, part (2) of claim 48, see lines 6-10, should be directed to a description of the claimed "modifying portion". However, lines 6-8 contain structural limitations for part (1)

of claim 48 such that "wherein the nucleic acid binding portion comprises an oligonucleotide or oligonucleotide mimic or analog". Appropriate correction is required.

2) Line 9 of claim 61 contains "SV4o", which appears to be a typographical error. It should be "SV40". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 73 and 74 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 73 and 74, as written, do not sufficiently distinguish over cells that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty,* 447 U.S. 303, 206 USPQ 193 (1980). The claim should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified", if supported by the instant specification. See MPEP 2105.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50 and 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 50 recites the limitation "wherein the repressor" in line 2, and claim 62 recites the limitation "wherein the nucleic acid binding portion and the repressor" in line 2. There is insufficient antecedent basis for this limitation in the claims because claim 48 does not recite the word "repressor".

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-57, 60-71, and 77-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting apoptosis in a cell comprising introducing a nucleotide *in vitro*, does not reasonably provide enablement for a method of promoting apoptosis in a cell *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation

such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the instant claims embraces both *in vitro* and *in vivo* embodiments, as evidenced by the disclosure of the instant specification. See for example pages 40-41, which discloses that the instantly claimed method of promoting apoptosis is intended to be applied in medicine such as for treating variety of cancers. Further, claims 65 and 66 are specifically directed to *in vivo* methods performed in an animal or a human, and claims 69-71 and 77-78 are directed to therapeutic methods and a pharmaceutical composition. As such, the claimed invention must be enabled for not only *in vitro* but also *in vivo* embodiments.

As of the earliest filing date sought in the instant application, which is December 5, 2002, nucleic acid-based therapy, so-called gene therapy, was considered unpredictable due to a number of various reasons. That is, the state of the art pertaining to the *in vivo* aspect of the instantly claimed invention was considered unpredictable. See for example Opalinska et al. (*Nature Reviews,* 2002, 1:503-514). On page 511, Opalinska et al. teach the unpredictability of nucleic acid molecules to inhibit the expression of their intended targets *in vivo* as following:

"Nucleic-acid-mediated gene silencing has been used with great success in the laboratory, and this strategy has also generated some encouraging results in the clinic. Nevertheless, it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA....Accordingly, mRNA targeting is largely a random process, which accounts for the many experiments in which the addition of an antisense nucleic acid yields no effect on expression." (emphasis added).

The unpredictability of *in vivo* inhibitory activity of oligonucleotides remained unresolved even after the earliest filing date sought in the instant case as evidenced by a post-dated reference (Patil et al., *American Association of Pharmaceutical Scientists Journal,* 2005, 7(1):E61-E77). Patil et al. warn against extremely low success of the introduction of DNA-based drugs for *in vivo* use. See page E62 for example, wherein Patil et al. teach the following: "Despite many favorable characteristics and signs of possible clinical victories (see Table 1), the introduction of DNA-based drugs for human use can be best described as limited, with rare successes. The inertia in the development of these drugs can be attributed, in part, to their poor cellular uptake profile *in vivo.* The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half-life result in unpredictable pharmacokinetics...The resulting random delivery profile of DNA-based drugs is further complicated by a lack of *in vivo/in vitro* correlation of their pharmacological outcomes."

As evidenced by the teachings of Opalinska et al. and Patil et al., delivering oligonucleotides into an appropriate target cell or tissue in an animal remained problematic in the art, and therefore it is concluded that the unpredictability of treating patients by administering an oligonucleotide was recognized in the art as of the earliest filing date sought in the instant application.

In order to overcome the art-recognized unpredictability and problems associated with gene therapy, the instant specification must provide sufficient teachings as to how to practice the claimed *in vivo* therapeutic methods. The instant specification, however, provides only prophetic and generic descriptions with regard to the *in vivo* therapeutic methods. That is, the instant specification is silent about specific direction/guidance commensurate in scope with the claimed *in vivo* methods. Note that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In view of the totality of the factors and the reasons stated above, one of ordinary skill in the art would not have been able to practice the entire scope of the claimed invention without undue experimentation at the time of the invention, and therefore the claims are rejected as failing to comply with the enablement requirement as set forth in the first paragraph, 35 U.S.C. 112.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 48, 51-54, 62-64, and 67-68 are rejected under 35 U.S.C. 102(a) as being anticipated by Lewis et al. (*Bioconjugate Chemistry,* 2002, 13:1176-1180).

The claims are drawn to a method of promoting apoptosis in a cell *in vitro* comprising introducing a molecule comprising an anti-Bcl2 antisense peptide nucleic acid is fused with a polypeptide.

Lewis et al. teach a method of promoting apoptosis in a cell comprising intracellularly delivering an anti-Bcl2 antisense PNA fused with a polypeptide. See the entire reference including Figure 1. Accordingly, all claim limitations are taught by Lewis et al.

Claims 48-50, 52-53, 55-56, 62-63, 67-68 are rejected under 35 U.S.C. 102(e) as being anticipated by Buluwela et al. (WO 03/010308 A2, applicant's citation).

The claims are drawn to a method of promoting apoptosis in a mammalian cell *in vitro* comprising introducing a molecule comprising a modifying portion fused to a nucleic acid binding portion.

Buluwela et al. teach a method of suppressing the expression of a selected endogenous gene such as oncogene or apoptosis-related gene (e.g., Ras) in a mammalian cell *in vitro* comprising introducing a molecule comprising a modifying portion and a nucleic acid binding

portion, wherein the modifying portion and the nucleic acid binding portion are fused or joined so that each portion retains its respective activity, wherein the nucleic acid binding portion is a DNA or RNA binding portion. They teach the modifying portion is chromatin inactivation or histone deacetylase complex portion such as HDAC or components of the HDAC complex, which results in the suppression of gene expression. See pages 4, 6-10, 24-28, 37-39; claims 1-8, 22, 30, 47. Since Buluwela et al. perform the active method step of suppressing the expression apoptosis-related genes such as Ras comprising introducing the claimed molecule into mammalian cells, the method of Buluwela et al. will inherently result in the promotion of apoptosis of the mammalian cells, absent evidence to the contrary. Accordingly, all claim limitations are taught by Buluwela et al.

Claims 48-56, 59, 62-63, and 67-68 are rejected under 35 U.S.C. 102(e) as being anticipated by Hart et al. (WO 03/033701 A1, applicant's citation).

The applied reference has common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are drawn to a method of promoting apoptosis in a mammalian cell *in vitro* comprising introducing a molecule comprising a modifying portion fused to a nucleic acid

binding portion, wherein the modifying portion is MAD1 and the nucleic acid binding portion is TFO or PNA.

Hart et al. teach a method of suppressing the expression of a selected endogenous gene such as an oncogene or apoptosis-related gene (e.g., Ras) in a mammalian cell *in vitro* comprising introducing a molecule comprising a modifying portion and a nucleic acid binding portion, wherein the modifying portion and the nucleic acid binding portion are fused or joined so that each portion retains its respective activity, wherein the nucleic acid binding portion is a DNA or RNA binding portion. They teach the modifying portion is chromatin inactivation or histone deacetylase complex portion such as HDAC or components of the HDAC complex such as MAD1, and the molecular mass is less than 11 kDa. They teach that the nucleic acid binding portion comprises an oligonucleotide analogue such as TFO and PNA. They teach that the molecule further comprises a nuclear localization signal peptide portion. See pages 3-8, 12-20, 31-33; claims 1-13, 17, 19-21. Since Hart et al. perform the active method step of suppressing the expression apoptosis-related genes such as Ras comprising introducing the claimed molecule into mammalian cells, the method of Hart et al. will inherently result in the promotion of apoptosis of the mammalian cells, absent evidence to the contrary. Accordingly, all claim limitations are taught by Hart et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 48-57, 60-65, and 67-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolffe et al. (WO 02/26960 A2, applicant's citation) in view of Reed (US 5,831,066) and Li et al. (*Genes & Development,* 2002, 16:687-692).

The claims are drawn to a method of promoting apoptosis in an animal cell *in vitro* comprising introducing into the cell a molecule comprising an oligonucleotide that binds to Bcl-2 and a MAD1 polypeptide, wherein the oligonucleotide is PNA, wherein the MAD1 polypeptide facilitates the recruitment of a HDAC complex and histone deacetylation, wherein the molecule further comprising SV40 NLS, wherein the oligonucleotide and the polypeptide are fused, wherein the oligonucleotide suppresses the expression of Bcl-2.

Wolffe et al. teach a method of repressing expression of a target gene in a cell *in vitro* by introducing a chimeric or fusion molecule comprising a triplex-forming oligonucleotide of a DNA binding domain that binds to a target site in the target gene and a polypeptide of a repression domain (e.g., HDAC-interacting proteins), wherein the chimeric or fusion molecule further comprises a nuclear localization signal SV40, wherein the target gene bcl-2, wherein the

triplex-forming oligonucleotide and the polypeptide are fused. See pages 5-6, 13, 30-31, 37, 41, 58-59, 68; claims 28-43. Wolffe et al. do not teach that their method induces apoptosis in a cell.

Reed teaches that inhibiting bcl-2 expression in cells, for example by introducing a bcl-2 antisense oligonucleotide, induces apoptosis of the cells, wherein the cells are tumor cells. See claims 8 and 21.

Li et al. teach that MAD1 is a repressor protein that interacts with Sin3 and recruits the HDAC1/2-containing Sin3 complex. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Wolffe et al. to induce or promote apoptosis in cells.

One of ordinary skill in the art would have been motivated to do so because Wolffe et al. taught the method of introducing a fusion molecule comprising a TFO targeted to bcl-2, a polypeptide comprising a HDAC-interacting protein, and a NLS SV40 to repress target gene (bcl-2) expression in a cell. Since inhibition of bcl-2 promotes apoptosis in cells as taught by Reed, the skilled artisan performing the method of Wolffe et al. would have necessarily obtained promotion of apoptosis in the experimental cells. Further, the skilled artisan would have been motivated to use a polypeptide comprising a repressor protein MAD1 as suggested by Wolffe et al. (suggested to use a HDAC-interacting repressor protein), because MAD1 is a HDAC-interacting protein as taught by Li et al. Since the framework of the claimed method including the method steps and materials was known and available in the art as taught by Wolffe et al., and the biological effect of bcl-2 inhibition (promotion or induction of apoptosis) was known in the art as taught by Reed, and since the inherent biological properties of MAD1 (interaction with HDAC1/2 and a repressor protein) were known in the art, the skilled artisan would have had a

reasonable expectation in combining the known steps and materials, which would have led the skilled artisan to arrive at the claimed invention. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635